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(54) Method of inhibiting microbial activity using insoluble dialdehyde polysaccharides

(71) Personal Products Company
(72) Siragusa, J.
(74) GH

(57) Claim 1. A composition for inhibiting bacterial growth on an animal including humans, by topically administering said composition on said animal, comprising a carrier suitable for topical administration and a bactericidally effective amount of a water-soluble dialdehyde polysaccharide selected from the group consisting of dialdehyde cellulose and dialdehyde starch wherein said water-insoluble dialdehyde polysaccharide has a degree of polymerization sufficient to render the dialdehyde polysaccharide water insoluble, said degree of polymerization being at least 50 repeating units per molecule.

Form 1
Regulation 9.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1969

APPLICATION FOR A PATENT

I/We, PERSONAL PRODUCTS COMPANY

of Milltown,
New Jersey,
U.S.A.

hereby apply for the grant of a Patent for an invention entitled "METHOD OF INHIBITING MICROBIAL ACTIVITY USING INSOLUBLE DIALDEHYDE POLYSACCHARIDES"

which is described in the accompanying complete specification

Our address for service is Messrs. Griffith, Hassel & Fraser, 323 Castlereagh Street, SYDNEY 2000, Australia.

Dated this 23rd day of May, 1977

PERSONAL PRODUCTS COMPANY
By their Patent Attorneys:

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED

of GRIFFITH, HASSEL & FRAZER.
(Fellows of the Institute of Patent Attorneys of Australia)

To: The Commissioner of Patents
Commonwealth of Australia.

AUSTRALIAN
24 MAY 1977
PATENT OFFICE

FEE STAMP TO VALUE OF $78 ATTACHED
MAIL OFFICER

COMMONWEALTH OF AUSTRALIA PATENT OFFICE $60 SIXTY DOLLARS
COMMONWEALTH OF AUSTRALIA PATENT OFFICE $16 SIXTEEN DOLLARS
COMMONWEALTH OF AUSTRALIA PATENT OFFICE $2 TWO DOLLARS

COMMONWEALTH OF AUSTRALIA
Patents Act 1952-1962

DECLARATION IN SUPPORT OF A CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

INSTRUCTIONS

(a) Insert No. if available

(b) Insert full name(s) of applicant(s).

(c) Insert title of invention

(d) Insert full name(s) of declarant(s) who must be PERSON or PERSONS, NOT a corporate body. (See head note).

(e) Insert address(es) of declarant(s).

(f) Delete entirely if applicant is corporate body.

(g) Delete entirely if applicant is person or persons.

(h) Delete entirely if Convention priority NOT claimed

(i) Insert country in which first basic application was filed

(j) Insert date of first basic application

(k) Insert full name(s) of basic applicant(s)

(l) Delete entirely if applicant(s) NOT inventor(s)

(m) Insert full name(s) of actual inventor(s) if applicant(s) NOT inventor(s)

(n) Insert address(es) of actual inventor(s) if applicant(s) NOT inventor(s)

(o) Recite manner in which applicant(s) derive(s) title from actual inventor(s) if applicant(s) NOT inventor(s)

(p) Delete entirely if Convention priority NOT claimed.

(q) Recite manner in which applicant(s) derive(s) title from basic applicant(s) if applicant(s) NOT basic applicant(s).

(r) Signature(s) of declarant(s).

(N.B.—No seal or stamp impression to be applied).

AUSTRALIA
24 MAY 1977
PATENT OFFICE

In support of the application No. (a).....

made by (b)... PERSONAL PRODUCTS COMPANY 25.4.31.177.....

for a patent/~~patent of addition~~ for an invention entitled (c)

"METHOD OF INHIBITING MICROBIAL ACTIVITY USING INSOLUBLE DIALDEHYDE POLYSACCHARIDES"

I, (d)... Michael Ryan, Secretary

of (e) ...501 George Street, New Brunswick, New Jersey, U.S.A.

do solemnly and sincerely declare as follows :—

1. (f) ~~I am/We are the applicant(s) for the patent/patent of addition~~

1. (g) I am authorised by the abovementioned applicant for the patent/~~patent of addition~~ to make this declaration on its behalf.

2. ~~The basic application(s) as defined by Section 141 of the Act was/were made in the~~ following country or countries on the following date(s) by the following applicant(s) namely :—

in (i)..... on (j)..... 19.....
by (k).....
in (i)..... on (j)..... 19.....
by (k).....
in (i)..... on (j)..... 19.....
by (k).....

3. ~~(l) I am/We are the actual inventor(s) of the invention.~~

3. (m)..Judith Siraguse.....

of (n)... R.D. #1 Hopewell, New Jersey, U.S.A.

is/~~are~~ the actual inventor(s) of the invention and the facts upon which the applicant(s) is/are entitled to make the application are as follows :—

—as regards entitlement under Section 34 of the Act :—(o). November 19, 1975 and March 17, 1977
The inventor assigned the said invention to the said applicant.

—as regards entitlement under Part XVI of the Act :—(q).....

4. The basic application(s) referred to in paragraph 2 of this Declaration was/~~were~~ the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at N.J., U.S.A. this 5th day of May, 1977

(r) Michael J. Ryan, Jr.

To : The Commissioner of Patents,
Commonwealth of Australia.

GRIFFITH, HASSEL & FRAZER Box 2133, G.P.O. SYDNEY 2001 AUSTRALIA

COMMONWEALTH OF AUSTRALIA

Form 10

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

25431/77

FOR OFFICE USE :

Class Int. Class

Application Number :
Lodged :

Complete Specification Lodged :
Accepted :
Published :

Priority :

Related Art :

TO BE COMPLETED BY APPLICANT

Name of Applicant : PERSONAL PRODUCTS COMPANY

Address of Applicant: Milltown,
New Jersey,
U.S.A.

Actual Inventor: Judith Siragusa.

Address for Service: Griffith, Hassel & Frazer,
323 Castlereagh St.,
SYDNEY N.S.W. 2000 AUSTRALIA

Complete Specification for the invention entitled: "METHOD OF INHIBITING MICROBIAL ACTIVITY USING INSOLUBLE DIALDEHYDE POLYSACCHARIDES"

The following statement is a full description of this invention, with the best method of performing it known to me/us:-

This invention relates to methods for inhibiting microbial activity. In particular, this invention relates to methods utilizing antimocrobial agents which are insoluble in aqueous media.

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According to the invention there is provided a composition for inhibiting bacterial growth on an animal including humans, by topically administering said composition on said animal, comprising a carrier suitable for topical administration and a bactericidally effective amount of a water-insoluble dialdehyde polysaccharide selected fron the group consisting of dialdehyde cellulose and dialdehyde starch wherein said water-insoluble dialdehyde polysaccharide has a degree of polymerization sufficient to render the dialdehyde polysaccharide water insoluble, said degree of polymerization being at least 50 repeating units per molecule.

U.S. Patent No. 2,801, 216 discloses that certain saturated lower dialdehydes possess batericidal activity toward sulfate-reducing bacteria. Also, alcoholic sporicidal compositions containing similar saturated lower dialdehydes are taught in U.S. Patent No. 3,016,328 . In addition, it is taught in U.S. Patent No. 3.679,792 that water-soluble dialdehyde starch can be incorporated into chewing gum compositions as a cariostatic agent which is released into the oral cavity upon mastication. In all of the foregoing instances the bactericidal or sporicidal agent is soluble and readily enters the medium which is susceptible to microbial growth. It has now been discovered, however , that effective inhibition of microbial activity can be achieved by means of dialdehyde polysaccharides which are

not soluble in the growth medium and thus do not exert a systemic effect on the medium.

Summary of the Invention

The present invention contemplates applying to a locus susceptible to microbial growth an effective amount of an insoluble dialdehyde polysaccharide sufficient to maintain an insoluble aldehyde content in the medium of at least about 0.1 weight percent. Microbial activity in wounds or lesions can be inhibited by topical treatment of the affected area with the aforesaid dialdehyde polysaccharide. Particularly preferred active ingredients for the purposes of the present invention are insoluble dialdehyde starch and dialdehyde cellulose having about 15 to about 100 percent of the 2,3 -hydroxyl groups thereof

oxidized to dialdehyde groups, that is, the insoluble dialdehyde polysaccharide contains at least about 6 weight percent aldehyde groups, based on the dialdehyde polysaccharide.

Detailed Description of the Preferred Embodiments

It has been found that water-insoluble dialdehyde polysaccharides such as water-insoluble dialdehyde starch and dialdehyde cellulose inhibit the growth of microorganisms with which these polysaccharides come in contact. Unlike other known antimicrobial agents which dissolve in or diffuse throughout a medium capable of sustaining microbial activity, the water-insoluble dialdehyde polysaccharides do not become part of the growth medium and thus do not alter the ecology thereof. This is a very desirable property because the antimicrobial agent thus does not enter the host system and is not absorbed by the host or by individuals who manufacture and/or administer the antimicrobial agents.

The water-insoluble dialdehyde polysaccharides can be incorporated into surgical or burn dressings, adhesive bandages, sanitary napkins, tampons, incontinence pads, disposable mattress pads, and can also be applied as a powder directly to an open wound or lesion. Furthermore, inasmuch as an inhibition of bacterial growth prevents the formation of malodors which are the normal metabolic products of growing microorganisms, the present method also provides a simultaneous deodorant effect.

The invention may be employed in inhibiting the growth of bacteria in vitro or in animals (for the purposes herein the term animals includes members of the animal kingdom including, ~~for example,~~ humans). In the case of in vitro use the water insoluble

dialdehyde polysaccharides may be homogeneously distributed throughout the medium or may be employed in contact with a surface of the medium. In the case of animals the dialdehyde polysaccharides may be administered topically or alternatively may even be administered orally. For example, when the inhibition of bacterial growth is directed toward preventing the formation of malodorous metabolic products in animals and in particular as a deodorant in humans, the dialdehyde polysaccharide may be employed in the form which deodorants are commonly found, e.g., in the form of a dusting powder or compounded with other ingredients in the form of a lotion, cream, stick or even spray-on deodorant.

The dialdehyde polysaccharides may be combined in any carrier suitable for topical application. When used as a dusting powder, the dialdehyde polysaccharide may be combined with other suitable powdered material such as cornstarch, talc, or the like. These mixtures may be employed alone or may be further modified with other inert powders such as zinc oxide or dicalcium phosphate. Lubricants or flow additives may be employed such as calcium and magnesium salts of fatty acids.

When used as a spray-on deodorant, the dialdehyde polysaccharide may be combined with the propellent liquids now known in the art as the fluorinated hydrocarbons commercially available under trade names such as Freons, Ucons, Genetrons, etc.

Liquid compositions, e.g., in a roll-on deodorant and solid compositions, e.g., a stick deodorant, are also usable wherein the dialdehyde polysaccharide is combined with suitable carriers such as water, alcohol, witch hazel in the case of liquids and waxes such as fatty amides (e.g., monoethanolamide of stearic acid, isopropanolamide of stearic acid) in the case of solids.

Suitable dialdehyde polysaccharides for the purposes of the present invention can be prepared by the selective oxidation of the 2,3-hydroxyl groups on the glucose units which make up the polysaccharide chain. Preferably, at least about 15 percent of the hydroxyl groups are oxidized, and more preferably about 35 to about 100 percent of the hydroxyl groups are oxidized. Inasmuch as the present invention contemplates water-insoluble dialdehyde polysaccharides, the degree of polymerization of the polysaccharide should be at least about 50 repeating units per molecule.

Methods for the aforesaid selective oxidation of polysaccharides to dialdehyde polysaccharides are known in the art. A particularly convenient method for this purpose involves oxidation by means of periodic acid as taught in U.S. Patent No. 3,086,969 to Slager. According to this method, a polysaccharide is reacted with a solution of periodic acid having a concentration of at least about 10 weight percent, based on the total amount of reactants present, in the presence of a strong acid which maintains the hydrogen ion concentration of the periodic acid solution at a pH below about 1.0. The reaction temperature usually is about 30°C. to 35°C.

The inhibition of microbial activity by the present method has been demonstrated in vitro and in vivo. The experimental results are reported hereinbelow.

EXAMPLE 1

Various samples of a quantity of polysaccharide powder comprising aldehyde polysaccharide are subjected to a variety of pretreatment steps and then each sample is added to molten nutrient agar at about 45°C. Each of the resulting admixtures is then dispensed onto sterile Petri plates and permitted to solidify. The surface of each solidified mixture is cross-streaked with about 0.01 milliliter aliquots of 18-hour broth cultures of various microbes constituting a broad spectrum which included both Gram positive and Gram negative Bacteria. Nutrient agar plates without any aldehyde polysaccharide powder are cross-streaked with the same broth culture and serve as controls. The inoculated plates are then incubated for 18 to 24 hours at a temperature of about 37°C. and examined to determine maximum growth of the test organisms. The samples of polysaccharide powder and the nature of their pretreatment are identified in Table I and the test results are reported in Table 2. The materials identified as cellulosic dialdehyde polysaccharides are prepared from ground woodpulp having an approximate degree of polymerization ranging from 500 to 2100. The materials identified as starch dialdehyde polysaccharides are prepared from waxy maize cornstarch having a degree of polymerization of about 1000. The resulting aldehyde polysaccharides have essentially the same degree of polymerization as the starting materials and are water insoluble.

The data in these tables show that broad spectrum antimicrobial activity against both Gram negative and Gram positive Bacteria was present as long as the total aldehyde

content of the test system is about 1.5 weight percent or more, and that Gram positive microorganisms are inhibited when as little as about 0.1 to 0.2 weight percent of the aldehydic material is present in the test system.

The data further shows that the antimicrobial activity of the dialdehyde polysaccharides is not lost by heating, washing in cold water, hot water, or with detergent.

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TABLE 1

IDENTIFICATION OF POLYSACCHARIDE SAMPLE

SAMPLE	COMPOSITION	PERCENT ALDEHYDE IN DIALDEHYDE COMPONENT [1]	PRETREATMENT
A	0.5 gm. dialdehyde starch -------	90 --------	Air dried to constant weight
B	0.5 gm. dialdehyde cellulose ----	85	do.
C	1.0 gm. dialdehyde cellulose ----	35	do.
D	0.5 gm. dialdehyde cellulose ----	66	do.
E	do.	66	do.
F	do.	66	do.
G	do.	66	Cold water washed and air dried
H	do.	54	Air Dried to constant weight.
I	do.	54	Cold water washed and air dried
J	do.	54	Dried at 100°C to constant weight
K	do.	54	Dried at 150°C to constant weight
L	do.	54	Hot water washed and air dried
M	do.	54	Hot water washed and dried at 100°C
N	do.	54	Detergent washed and air dried
O	0.25 gm. wood pulp [2] and 0.25 gm. dialdehyde cellulose	80	Blended and air dried
P	0.5 gm. dialdehyde cellulose	35	Air dried to constant weight
Q	0.25 gm. wood pulp [2] and 0.25 gm. dialdehyde cellulose	66	Blended and air dried.
R	do.	54	do.
S	0.5 gm. dialdehyde cellulose	19	Air dried to constant weight.
T	do.	10	do.
U	0.25 gm. wood pulp [3] and 0.25 gm. dialdehyde cellulose	10	Blended and air dried
V	0.38 gm. wood pulp [3] and 0.12 gm. dialdehyde cellulose	10	do.
W	0.43 gm. wood pulp [3] and 0.07 gm. dialdehyde cellulose	10	do.
X	0.47 gm. wood pulp [3] and 0.03 gm. dialdehyde cellulose	10	do.
Y	0.50 gm. wood pulp [2] -----	0	Air dired to constant weight.
Z	0.50 gm. wood pulp [3] -----	0	do.

1) percent aldehyde refers to percent of 2, 3 hydroxyl groups which have been oxidized based on total polysaccharide in the sample.

2) fully bleached Southern Pine kraft pulp (fluff) obtained from Buckeye Cellulose Co.

3) bleached chemical wood pulp, finely ground (particle size 50-70 microns) obtained from Brown Co. Berlin, N.H., sold by them under trade name Solka-flox.

SUMMARY OF ANTIMICROBIAL SCREENING

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Sample	Aldehyde Concentration in Test System [1]	Organisms Treated				
		P.mirabilis	S.aureus	St.fecalis	E.coli	A.aerogenes
A	4.3	N.T	+	+	0	0
B	4.0	+	N.T	N.T	N.T	N.T
C	3.2	N.T	+	+	+	+
D	3.1	N.T	+	+	+	+
E	3.1	+	+	+	+	+
F	3.1	+	+	+	+	+
G	3.1	N.T	+	+	+	+
H	2.6	N.T	+	+	+	+
I	2.6	N.T	+	+	+	+
J	2.6	N.T	+	+	+	+
K	2.6	N.T	+	+	+	+
L	2.6	+	+	+	+	+
M	2.6	+	+	+	+	±
N	2.6	+	+	+	+	+
O	1.9	N.T	+	+	+	±
P	1.7	N.T	+	+	+	0
Q	1.6	N.T	+	+	0	+
R	1.3	+	+	+	0	0
S	0.9	+	+	+	0	0
T	0.5	0	+	+	0	0
U	0.25	N.T	+	+	0	0
V	0.12	N.T	+	+	0	0
W	0.062	N.T	0	0	0	0
X	0.031	N.T	0	0	0	0
Y	0.0	0	0	0	0	0
Z	0.0	N.T	0	0	0	0

+ = total inhibition; ± = slight inhibition; 0 = no inhibition; N.T. = not tested

1) aldehyde concentration is calculated on the basis of the reported aldehyde content of the test material as a function of the total weight of test sample plus nutrient agar.

EXAMPLE 2

Antibacterial Paper dressing

A paper handsheet was prepared from a blend of dialdehyde cellulose (50 weight percent dialdehyde cellulose /80% aldehyde/ and 50 weight percent wood pulp).

Petri plates containing 10 ml. of Trypticase soy agar were prepared with the agar surface cross-streaked with test bacteria including S. aureus and P. mirabilis. A square piece of the test hand sheet (1 inch x 1 inch) was then placed onto the innoculated agar surface and incubated for about 18 to 24 hours. Surface inhibition of S. aureus and P. mirabilis was observed, as well as a slight zone of inhibition against S. aureus.

EXAMPLE 3

Wound Treatment with Dialdehyde Cellulose

The tails of three newborn Pembroke Welsh Corgi puppies were amputated. Two days later, two of the puppies were observed to have an infection in the amputated region. A bloody purulent discharge, as well as swelling of the tail stump was noted. Hot compresses were applied to the infected area at regular intervals for about one day, but no improvement was observed. Thereafter, dialdehyde cellulose powder (80% aldehyde; particle size about 60 to 80 microns) was sprinkled onto the stump of one of the puppies while the other received no further treatment. One day later the dialdehyde cellulose-treated stump was no longer swollen or moist, and the flesh had a clean appearance. The untreated stump, on the other hand, was still swollen and moist, and the same purulent exudate was present.

EXAMPLE 4

Washing of Dialdehyde Cellulose

A sample of dialdehyde cellulose (Sample H) was washed under various conditions as shown in Table 3 below, and the obtained washings were tested for antimicrobial activity in a manner similar to Example 1 above. No inhibition of bacterial growth by the washings was observed. Thus, the sterilizing properties of the dialdehyde polysaccharides are indigenous to the water-insoluble oxidized polysaccharide itself.

TABLE 3

WATER WASHING EXPERIMENTS WITH DIALDEHYDE CELLULOSE*

Wt. of Sample (grams)	Volume of Water (ml)	Length of Time (hours)	Temperature (°C.)	Apparatus Used
0.5	5	0.16	20	Beaker with stirrer
7.0	200	7.00	100	Soxhlet extracter
0.5	5	20.00	20	Beaker with stirrer

* Sample H

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A composition for inhibiting bacterial growth on an animal including humans, by topically administering said composition on said animal, comprising a carrier suitable for topical administration and a bactericidally effective amount of a water-insoluble ~~water-soluble~~ dialdehyde polysaccharide selected from the group consisting of dialdehyde cellulose and dialdehyde starch wherein said water-insoluble dialdehyde polysaccharide has a degree of polymerization sufficient to render the dialdehyde polysaccharide water insoluble, said degree of polymerization being at least 50 repeating units per molecule.

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2. A composition of Claim 1 wherein said water-insoluble dialdehyde polysaccharide contains at least about 6 weight percent aldehyde groups based on the weight of said aldehyde polysaccharide.

3. A composition of Claim 1 wherein said water-insoluble dialdehyde polysaccharide is water-insoluble dialdehyde starch .

4. A composition of Claim 1 wherein said water - insoluble dialdehyde polysaccharide is water-insoluble dialdehyde cellulose.

Dated this 31st day March, 1980

PERSONAL PRODUCTS COMPANY
By their Patent Attorney

GRIFFITH, HASSEL & FRAZER